Bandolier 65

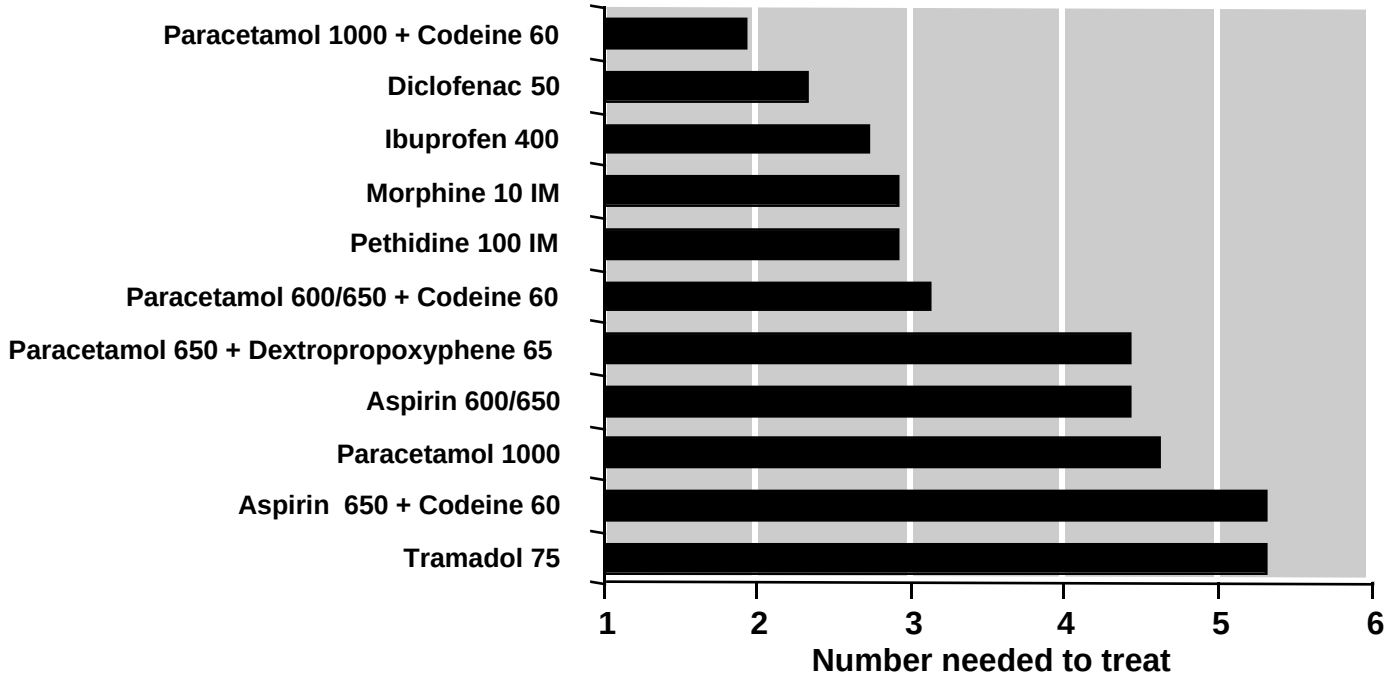
What do we think?
What do we know?
What can we prove?

Evidence-based health care **£3.00** **July 1999 Volume 6 Issue 7**

Oxford Pain Internet Site

This month, on July 14th, ***Bandolier*** is opening the Oxford Pain Internet Site. The content is different from the usual ***Bandolier*** story which gives a view on a systematic review or trial. Instead the site provides formal summaries of systematic reviews looking at pain outcomes. Each précis has a clinical bottom line at the top, followed by a commentary taking about five minutes to read if you want more information. There are NNTs and L'Abbé plots when they can be calculated or drawn, with references for further reading to other, similar, reviews, as well as links to related pages on the site. An example is shown on page 2 for a systematic review of antidepressants in neuropathic pain.

There is also the Oxford League Table of analgesic effectiveness. This shows the relative efficacy of single-dose analgesics in acute pain, using the number needed to treat for at least 50% pain relief over 4 to 6 hours compared with placebo for patients with moderate or severe pain. The NNTs have been obtained from randomised, double-blind trials, all of which have used standard pain efficacy measures in standard pain models (mostly after molar extraction or in postoperative pain). So there is a standard method, in patients with the same condition, using standard outcomes obtained by standard scales and using the same standard comparator, placebo.



Information is available for 18 drugs used at some 50 different doses. The full information is on the Internet edition, but a summary of the NNTs for the most common analgesics is shown in the Figure and in the Table on page 8, which also has confidence intervals and numbers of patients. Oral NSAIDs perform as well as intramuscular opioids and oral combinations of simple analgesics and opioids.

Of course, this is not the complete picture. Adverse effects, cost and the requirements of individuals and institutions are also part of the decision-making process. Some information on adverse effects, in both acute and chronic use is also presented on the Internet site.

In this issue

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ANTIDEPRESSANTS IN NEUROPATHIC PAIN

Clinical bottom line: Antidepressants are effective in reducing neuropathic pain. The overall NNT for at least 50% pain relief for antidepressant compared with placebo in diabetic neuropathy was 3.0 (2.4 to 4.0) and was similar across pain conditions. 30% of patients will obtain more than 50% pain relief, 30% will have minor adverse reactions and 4% will have to stop treatment because of major adverse effects. SSRIs may be as effective, but are associated with a 50% reduction in major adverse reactions.

Antidepressants in neuropathic pain

Antidepressants have been used for over 30 years to manage neuropathic pain, but in the UK no antidepressant has a product licence for this indication. Although many studies have been carried out, it remains difficult to determine, for example, which antidepressant is most effective, or that antidepressants are better than anticonvulsants. What is clear is that antidepressants have an analgesic effect on top of any mood effect.

Systematic review

HJ McQuay, RA Moore. An evidence-based resource for pain relief. Oxford University Press March 1998 ISBN 0-19-262718-X.

Date review completed: 1994

Number of trials included: 18 (21 placebo-controlled arms / 11 active controls)

Number of patients: 400 active versus 373 placebo controls.

Control group: placebo or active (antidepressant / analgesic / anticonvulsants / tranquillisers)

Main outcomes: Relative benefit and NNT to achieve at least 50% pain relief (with 95% confidence intervals).

Inclusion criteria were randomised controlled trials of antidepressants in neuropathic pain (including diabetic neuropathy, postherpetic neuralgia, atypical facial pain and central pain); placebo or antidepressant or 'other intervention' control group; full journal publication; group size at least 10; pain outcome.

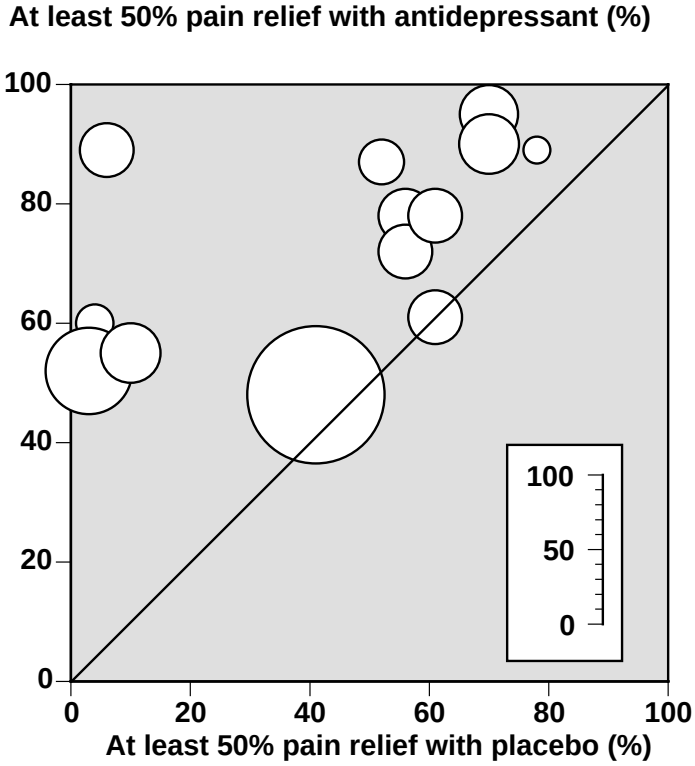
A clinically relevant outcome was defined as a measure equivalent to at least 50% pain relief, and outcomes of the longest duration were selected.

Placebo-controlled comparisons

Diabetic neuropathy

Six of 13 comparisons in diabetic neuropathy showed significant improvement over placebo (covering nine different antidepressants, Figure). Desipramine and tricyclics produced the best NNTs. The overall NNT was 3.0 (2.4 to 4.0).

Figure: At least 50% pain relief with antidepressant compared with placebo in diabetic neuropathy



Postherpetic neuralgia

Two of three comparisons in post-herpetic neuralgia showed significant benefit The combined NNT was 2.3 (1.7 to 3.3).

Atypical facial pain

Two of two comparisons in atypical facial pain showed significant benefit. The combined NNT was 2.8 (2.0 to 4.7)

Central pain

Only one of three trials had extractable data, with an NNT of 1.7 (1.1 to 3.0) in a small number of patients.

Active-controlled comparisons

In three of three reports tricyclics were significantly more effective than benzodiazepines. Two of two reports showed no differences between various tricyclics.

Table: NNT and relative benefit for antidepressants compared with placebo for neuropathic pain conditions

Condition	Number of trials	Antidepressant improved/total	Placebo improved/total	NNT (95%CI)
Diabetic neuropathy	13	180/260	73/205	3.0 (2.4 to 4.0)
Postherpetic neuralgia	3	43/77	8/68	2.3 (1.7 to 3.3)
Atypical facial pain	2	62/88	30/85	2.8 (2.0 to 4.7)
Central pain	1	10/15	1/15	1.7 (1.1 to 3.0)

Many of the trials demonstrated analgesic benefit without significant changes in mood measures. There was no difference in efficacy across different pain conditions. Although only one trial compared antidepressants with anticonvulsants directly. This showed greater benefit at lower risk with antidepressant.

Adverse effects

The number needed to harm (NNH) for minor adverse effects was 3.7 (2.9 to 5.2) based on 11 reports, combining across pain syndromes. For major effects the NNH was 22 (14 to 58), based on 19 reports. Effects were lower for SSRIs (fluoxetine and paroxetine) than with tricyclics.

Related topics

Anticonvulsants in chronic pain
Topical capsaicin
NNT
Relative benefit/risk

Further reading

The current review is an expansion of:

McQuay HJ, Tramer M, Nye BA, Carroll D, Wiffen PJ, Moore RA. A systematic review of antidepressants in neuropathic pain. Pain. 1996; 68: 217-227.

The following review covers a similar area, but includes headache:

France RD, Houpt JL, Ellinwood EH. Therapeutic effects of antidepressants in chronic pain. Gen Hosp Psychiatry. 1984; 6: 55-63.

Other reviews on this topic:

Goodkin K, Vrancken MA, Feaster D. On the putative efficacy of the antidepressants in chronic, benign pain syndromes. An update. Pain Forum. 1995; 4: 237-247.

Lee R, Spencer PS. Antidepressants and pain : a review of the pharmacological data supporting the use of certain tricyclics in chronic pain. Journal of International Medical Research. 1977; 5: 147-156.

Max, M. B. Thirteen consecutive well-designed randomized trials show that antidepressants reduce pain in diabetic neuropathy and postherpetic neuralgia. Pain Forum. 1995; 4(4): 248-253.

Onghena P, Van Houdenhove B. Antidepressant-induced analgesia in chronic non-malignant pain: a meta-analysis of 39 placebo-controlled studies. Pain. 1992; 49: 205-19.

Turner JA, Denny MC. Do antidepressant medications relieve chronic low back pain? J Fam Pract. 1993 Dec; 3: 545-53.

HIGH ON HIGH

Into thin air; A Personal Account of the Mt. Everest Disaster ; Jon Krakauer, *Anchor ISBN 0-385-49208-1*, £4.62 at Internet book shop

Faced with the question "What is my oxygen saturation on a transatlantic Jumbo after a couple of drinks?" ***Bandolier*** has found a partial answer, in a review by Andrew Peacock (BMJ 1998;317:1063). "Commercial aircraft are pressurised but only to an altitude of 1800 to 2500 m, and inspired oxygen pressure will be lower than at sea level. This usually has little effect because patients do not exercise during the flight. However, in some patients the reduction in inspired oxygen pressure is critical and additional oxygen may be necessary. As a rule of thumb patients should have an arterial oxygen pressure breathing air greater than 9 kPa at sea level to give them an PaO_2 at 1500 m above 6.7 kPa."

Into thin air is the story of an Everest expedition in 1996. The effects of hypoxia, on judgement and performance, are described in an enthralling and horrifying account. Just like most medical disasters, there was layer on layer of mistake before the inevitable became irretrievable. But that is just how medical, and other, accidents often occur. It isn't just one big thing going wrong - though that happens - but more often the accretion of little things going wrong.

This book is thrilling, terrifying and recommended.

Sexual dysfunction survey

As medicine and lifestyle become inextricably mixed, dealing with issues concerning sexual dysfunction is more common. The explosion of interest in male erectile problems is just one part of this, so any study which sheds more light on just how common problems are is helpful.

Study

As part of a US National Health and Social Life Survey, questions were asked of men and women aged between 18 and 59 years [1]. There were 1410 men and 1749 women, with exclusions of people living in group quarters (barracks, dormitories, prisons) and people not fluent in English. Seventy-nine percent of people asked took part in the survey.

Results

The answers for six questions given to both men and women are shown in the Table. For most questions there was little difference in response rates with age, except pain during sex (higher in the youngest age group of women), sex not pleasurable (lowest in the oldest age group of women), and trouble achieving or maintaining an erection (increased with age in men, Figure).

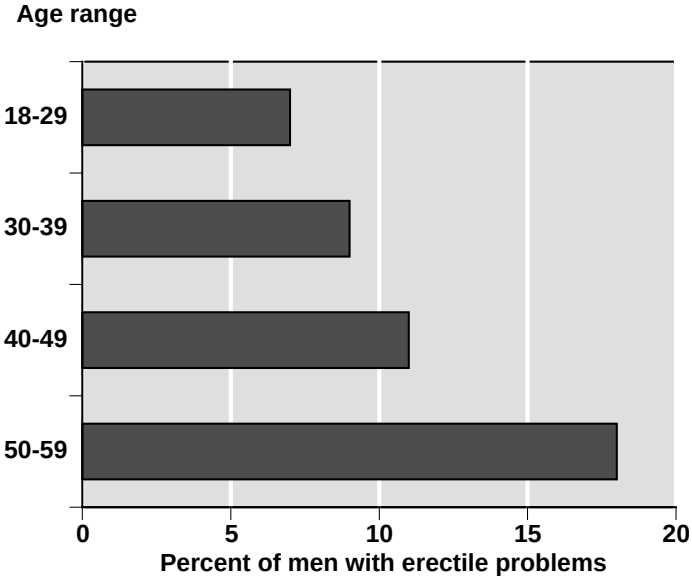
Clearly there was a high overall rate of problems, with 32% of women lacking interest in sex, 26% unable to achieve orgasm and 16% experiencing pain during sex. For men, early climax and anxiety about performance were major problems, but in the age group of 50-59 years 18% had trouble achieving or maintaining an erection.

The study also showed that the experience of sexual dysfunction is highly associated with unsatisfying personal experiences and relationships. There were strong (and probably causal) relationships between low sexual desire or performance with low physical and emotional satisfaction and low general happiness.

Table: Responses to questions about sexual dysfunction in men and women aged 18-59 years in the USA

Question	Percent
Women	
Lack interest in sex	32
Unable to achieve orgasm	26
Experience pain during sex	16
Sex not pleasurable	23
Anxious about performance	12
Trouble lubricating	21
Men	
Lack interest in sex	15
Unable to achieve orgasm	8
Climax too early	31
Sex not pleasurable	8
Anxious about performance	18
Trouble achieving or maintaining erection	10

Figure: Percentage of men with erectile problems at different ages.



Comment

When clever chemists, by chance or design, develop safe and effective drugs which help women achieve an orgasm, or which relieve pain during sex, then there will be a stampede to obtain those drugs, just as there has been for effective treatments for male erectile dysfunction. For many people poor sexual life translates into lower general happiness.

Given that most people recognise that life is not a rehearsal, but the real thing, and that sexual problems are common, then you don't have to be a rocket scientist to see this as a major growth area. In the UK, and probably in other countries, some imaginative solutions will be needed to how we deal with lifestyle, health and medical resources.

Reference:
1 EO Laumann, A Paik, RC Rosen. Sexual dysfunction in the United States: prevalence and predictors. JAMA 1999 281: 537-544.

Sildenafil and erectile dysfunction in diabetes

Bandolier 53 reported on some of the first trials of sildenafil (Viagra). Those trials recruited patients with erectile dysfunction caused by a range of conditions. Only about 14% of the men had diabetes. A new report [1] concentrates on men with diabetes.

Study

It was conducted in 268 men with a mean duration of erectile dysfunction of 5.6 years with type I or type II diabetes

with a mean duration of 12 years since diagnosis. The mean age was 57 years with a range of 27 to 79 years.

The study was properly randomised and double blind, and compared sildenafil against placebo over 12 weeks. The sildenafil dose was 50 mg initially, but could be increased to 100 mg or decreased to 25 mg. There were various obvious exclusions. Men with haemoglobin A1c values of more than 12% and a fasting plasma glucose of more than 16.6 mmol/L before the trial started were excluded.

Outcomes

The basic method used in the sildenafil study was that of a self-administered measure of erectile dysfunction, the international index of erectile dysfunction (IIEF) which was detailed in ***Bandolier*** 53. Results on efficacy were taken from questions 3 ("When you attempted sexual intercourse, how often were you able to penetrate your partner?") and question 4 ("During sexual intercourse, how often were you able to maintain an erection after you had penetrated your partner?") of the IEFF index.

Results

At baseline, and after 12 weeks with placebo, the mean responses to questions 3 and 4 were at the level of "much less than half the time". After 12 weeks with sildenafil the mean responses were above the level of "about half the time". This response rate was similar to that of 50 mg of sildenafil found in the earlier studies (***Bandolier*** 53).

Successful sexual intercourse was reported by 48% of men on sildenafil and 12% of men on placebo during the last four weeks of treatment. Improved erections were reported by 74/131 men on sildenafil and 13/127 patients taking placebo. This gives a number needed to treat of 2.2 (95% confidence interval 1.8 to 2.8)

Adverse effects

More men taking sildenafil reported headache (11%) and dyspepsia (9%), as well as some respiratory tract disorders (6%), flushing (4%), rhinitis (4%) and abnormal vision (4%). Adverse effects were found in 22/136 men on sildenafil and 1/132 men taking placebo. The number needed to harm was 6.5 (4.6 to 11). Cardiovascular adverse effects occurred in 4/136 men on sildenafil and 6/132 men taking placebo.

Comment

The results for men with diabetes (predominantly type II) were much the same as those in men with other causes of their erectile dysfunction (***Bandolier*** 53). The effectiveness of sildenafil was much the same irrespective of age, duration of erectile dysfunction or duration of diabetes.

Reference:

1 MS Rendell et al. Sildenafil for treatment of erectile dysfunction in men with diabetes. JAMA 1999 281: 421-426.

Correspondence on Laxatives

Dear *Bandolier*

Some time ago you ran a piece on the lack of RCTs on the subject of laxative prescribing. This, and some work in a local practice, prompted Shropshire Primary Care Audit Group to conduct an audit on the subject.

Twenty-one Shropshire practices took part in a retrospective audit of prescribing of stimulant laxatives. Each practice counted the number of patients having repeat prescriptions for stimulant laxatives and then reviewed the notes of ten patients.

Prescribing rates varies from 0.1% to 4.2% of patients across the 21 practices (mostly below 1%); 1302 of 170,479 patients were taking regular stimulant laxatives, a prescribing rate of 0.76%. Half the prescribing was in people aged 71 years and older, but a small but significant proportion was in children under 16 years.

There were several pieces of good news coming from the audit:

- The majority of patients (72%) had had their medication reviewed in the last year and/or had been examined.
- About 30% had been advised about other methods of relieving constipation and/or had been told what to do in the event of rectal bleed or change in bowel habit.
- The audit identified 12 children under 16 years who had been on stimulant laxatives for a mean of 3.8 years (predominantly for constipation). This meant that prescribing could be reviewed.
- The practice with the highest prescribing rate investigated prescribing and showed it was due mainly to poor nursing home practices. The residents of two nursing homes had diets inadequate in fibre, little or no exercise, and in many cases were unnecessarily catheterised. The practice has exerted influence on these homes to improve care of residents and instituted systems to prevent recurrence of over-prescribing.

The moral of this tale is that ***Bandolier*** obviously reaches parts other journals cannot.

Yours sincerely

Dr Jane Rees
Medical Advisor to PCAG

The full audit results are published on the ***Bandolier*** Internet site in ***Bandolier*** Internet publications. It can be found on www.jr2.ox.ac.uk/Bandolier/bandopubs/bandopubs.html, together with other material not published in paper evrsions of ***Bandolier.***

EVIDENCE-BASED VEGETABLES AND DIABETES

Bandolier is intrigued by high-quality studies associating behaviour, especially eating and drinking, with health outcomes. Such studies cannot prove a link, merely suggest an association. There may be confounding variables or factors which no-one has yet thought of, and links may not be causal.

But when consistent patterns emerge linking a type of behaviour with good health outcomes, and when the "definitive" randomised trial may never be done, we have to ask ourselves when the evidence is sufficient for us to change our behaviour. That may include not only the strength of the evidence available, but also our own hopes, fears, and biases. We may fear cancer more than heart disease, or diabetes more than both.

There ***is*** bias in this. ***Bandolier*** is a fan of vegetables and salads (and chips, but don't mention that). So notice is taken of a study associating year-round consumption of salad vegetables with reduced risk of diabetes [1], especially when the study is large and good.

Study

This was part of the Isle of Ely Study (run from Cambridge) which is prospectively studying the aetiology of type II diabetes. From a randomly-selected sample of the population age 40 to 64 years, and after excluding people with diabetes or who had moved away, 1122 people (73% of those asked to participate) were included in the study. They came to a screening centre and underwent a standard 75 g oral glucose tolerance test, had lots of questions asked and measurements made, and particularly answered a battery of questions about their food consumption.

Data on the frequency of consumption of foods was coded into the broad areas of frequent (daily consumption of food on most days) and infrequent. Fruit, salad and raw vegetables were divided into the broad groups of frequent all year, frequent in summer only, and infrequent all year.

Results

There were 51 people (4.5%) who had non-insulin dependent diabetes mellitus (NIDDM) by WHO criteria, and 188 (17%) who had an impaired glucose tolerance test. Age-standardised rates were 2.3% and 11.2% respectively. These people were older, fatter and less active than those with normal glucose tolerance tests.

People who ate salad vegetables frequently all year had a lower incidence of impaired glucose tolerance (13%) than those who ate them less frequently (17%). Most impressive, though, was the incidence of NIDDM (Figure), which was only 1% in people eating salad vegetables frequently throughout the year, compared with almost 6% with those eating them infrequently throughout the year.

The results for salad vegetable consumption remained significant after various adjustments. It was apparent in people who were not overweight. Frequent fruit consumption was not significantly associated with lower diabetes incidence.

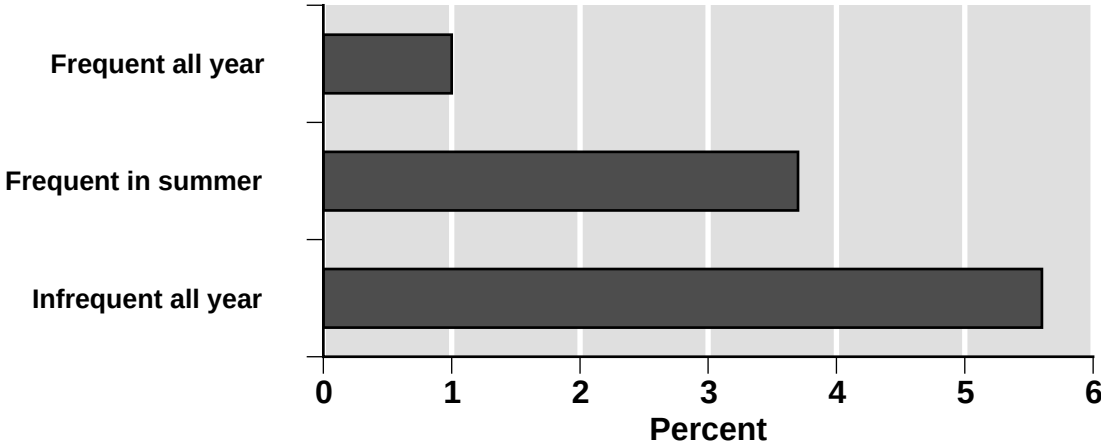
Comment

Another brick in the wall for evidence-based health eating and healthy living. Evidence associating vegetable consumption as protective against bad things happening to an individual's health continues to build. Eating vegetables seems to protect against heart disease and stroke, probably protects against some forms of cancer, and now is implicated in protecting against the development of diabetes.

It would be interesting to speculate whether significant shifts in healthy living behaviour would contribute to reduced healthcare demands. If cardiovascular disease, cancer and diabetes are major consumers of health care resources, and the incidence of these diseases fell because we all ate more vegetables, what would we die of? Would we just consume more social services instead? Someone must have modelled this.

1 DE Williams et al. Frequent salad vegetable consumption is associated with a reduction in the risk of diabetes mellitus. Journal of Clinical Epidemiology 1999 52: 329-335.

Figure: Incidence of diabetes according to the consumption of salad and raw vegetables



HELICOBACTER AND DYSPEPSIA

Most people have dyspepsia at some time or another, and in the USA between 2% and 5% of all GP visits are for dyspepsia. When Helicobacter pylori infection of the stomach became established as a prime cause of peptic ulcers, it was hypothesised that eradication of the bacterium would not only cure ulcers, but also be beneficial for many people with dyspepsia. The problem was that most trials examining this question were flawed. Most did not even use an effective eradication regimen.

Two excellent studies [1,2] have now been published which compare the effectiveness of Helicobacter eradication with a short course of proton pump inhibitor, and which look at long-term (12-month) outcomes after eradication therapy in nonulcer dyspepsia. Both were randomised, double-blind and double-dummy. Both followed intensive clinical and endoscopic assessment of patients including multiple tests for Helicobacter pylori, clinical evaluations, and initial and follow-up endoscopy. They come to (apparently) different conclusions.

Study 1 [1]

This MRC-sponsored study in Glasgow enrolled 318 patients to receive omeprazole plus antibiotics or omeprazole alone for two weeks. The main endpoint was resolution of symptoms 12 months after treatment.

Study 2 [2]

The second study was jointly funded by The Swiss National Foundation and Astra, was multi-centre, and enrolled 328 patients to receive omeprazole plus antibiotics or omeprazole alone for one week. The main endpoint was relief of dyspeptic symptoms at 12 months after treatment.

Results

Eradication of Helicobacter pylori was about 80% or more with eradication therapy, and low with omeprazole alone.

The main outcomes for each trial are shown in the Table, together with the overall results of both trials combined. One trial [1] showed a statistical improvement for symptoms at 12 months. The other [2] did not. Overall, ten patients had to be given a short course of omeprazole plus antibiotics for one to have symptomatic relief from dyspepsia at 12 months who would not have had symptomatic relief with omeprazole alone.

For healing of gastritis, the NNT with omeprazole plus antibiotics was 1.4 (95% confidence interval 1.3 to 1.5).

Comment

Why should one trial be positive and the other not? It may be that the populations being treated had different conditions, as an accompanying editorial suggests [3]. It may also be random chance. Both trials, and the combined result, show a moderate effect, mirrored in one [1] by reduced prescribing of antisecretory medicines. Then there is the way in which symptoms were scored. One study [2] used a score of 0 or 1 out of a scale of 0 to 7, while the other [1] used a score of 0 or 1 out of a scale of 0 to 20.

Is there enough here to make a judgement about treatment guidelines for dyspepsia? The answer is that on this evidence there is probably not. We would need a systematic review which would include at least one other high quality trial which has been done (and is reportedly positive), plus an economic evaluation, plus some supporting evidence to make a judgement.

The economic analysis would need to balance need for endoscopy (a significant proportion of patients would be over 45 years, when endoscopy is recommended) against lower costs of prescribed antisecretory medicines. The human analysis might take into account that eradication treatment is likely to prevent development of some peptic ulcers. But for now it seems to be "watch this space".

References:

1 K McColl et al. Symptomatic benefit from eradicating Helicobacter pylori infection in patients with nonulcer dyspepsia. New England Journal of Medicine 1998 339: 1869-1874.

2 AL Blum et al. Lack of effect of treating Helicobacter pylori infection in patients with nonulcer dyspepsia. New England Journal of Medicine 1998 339: 1875-1881.

3 LS Friedman. Helicobacter pylori and nonulcer dyspepsia. New England Journal of Medicine 1998 339: 1928-1930.

Table: Dyspepsia and eradication of Helicobacter pylori - individual trials and overall results.

Outcome	McColl et al [1]	Blum et al [2]	Combined
Success with omprazole (%)	7	21	**14**
Success with antibiotics & omeprazole (%)	21	27	**24**
NNT for one-year success	7.3 (4.7 to 17)	15 (6.3 to -40)	**9.9 (6.2 to 25)**
NNT for one-year healed gastritis		1.4 (1.3 to 1.5)	**1.4 (1.3 to 1.5)**

NNTs for at least 50% pain relief obtained from randomised, single-dose, double-blind trials using standard pain efficacy measures in standard pain models, using standard methods, in patients with the same condition, using standard outcomes obtained by standard scales and using the same standard comparator, placebo.

Drug or combination	Route	NNT (95% CI)	Number of patients in comparison
Paracetamol 1000 mg + Codeine 60 mg	Oral	1.9 (1.5 to 2.6)	127
Diclofenac 50 mg	Oral	2.3 (2.0 to 2.7)	636
Ibuprofen 400 mg	Oral	2.7 (2.5 to 3.0)	2898
Morphine 10 mg	Intramuscular	2.9 (2.6 to 3.6)	946
Pethidine 100 mg	Intramuscular	2.9 (2.3 to 3.9)	364
Paracetamol 600/650 mg + Codeine 60 mg	Oral	3.1(2.6 to 3.9)	816
Aspirin 600/650 mg	Oral	4.4 (4.0 to 4.9)	5061
Paracetamol 650 mg + Dextropropoxyphene (65 mg hydrochloride or 100 mg napsylate)	Oral	4.4 (3.5 to 5.6)	963
Paracetamol 1000 mg	Oral	4.6 (3.9 to 5.4)	2283
Aspirin 650 mg + Codeine 60 mg	Oral	5.3 (4.1 to 7.4)	598
Tramadol 75 mg	Oral	5.3 (3.9 to 8.2)	563

FEVERFEW FOR MIGRAINE

A systematic review [1] reports evidence that feverfew is effective for prophylaxis against migraine attacks.

Search

Randomised, double-blind placebo-controlled trials were sought using feverfew for the prevention of migraine. Searching was comprehensive, included asking manufacturers for unpublished studies, and papers were included only if feverfew was used alone.

Results

Five studies were found, one of which was published only as an abstract.

Two crossover trials (70 patients total, one an abstract looking at serotonin uptake and platelet activity) showed no effects over 2-4 months. Three other trials, (146 patients, one parallel group, the other two crossover trials) found significant reductions in the attack frequency, pain intensity, and incidence and/or severity of nausea and vomiting.

No meta-analysis was possible because of the disparate outcome measures used in the trials. The level of statistical significance reported in the positive trials was usually high, and often beyond 1 chance in 50.

Adverse effects

Adverse effects were mild and reversible.

Comment

Such information as is available from high-quality trials favours feverfew over placebo for the prevention of migraine headaches. The effectiveness of feverfew has not been established beyond reasonable doubt. The very high levels of statistical significance found in the positive trials suggest that larger studies looking at standardised feverfew extracts would make sense especially with the low level of adverse effects.P

Reference:
1 BK Vogler, MH Pittler, E Ernst. Feverfew as a preventive treatment for migraine: a systematic review. Cephalalgia 1998 18: 704-708.

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